REMARKS

Claims 1-9, 11-35, 38-39 and 42-46 were pending in this application. Claim 7 has been canceled without prejudice to pursuing this claim in a continuing application. Claims 1, 8, 11-12, 20-21, 27, 35, 42-43 and 45-46 have been amended and claims 47-48 are new. Upon entry of these amendments, claims 1-6, 8-9, 11-35, 38-39 and 42-48 will be pending and under active consideration. A marked version of the claims indicating the changes to the claims is attached hereto as Exhibit A. A copy of all the claims, as amended, is attached hereto as Exhibit B.

Applicants have amended claims 1 and 12 to correct a typographical error, wherein the method is now directed to a method of "preparing" a composition. Applicants have also amended claims 1 and 12 to recite "debulking the suspension based on cell size, buoyant density, or a combination thereof to remove mature cells." Applicants have amended claims 11-12, 20-21 and 42-43 to the recite that the progenitors are "hepatic." Applicants have amended claims 11, 20-21 and 42-43 to recite that the progenitors are "pluripotent." Applicants have amended claims 27 and 35 to correct a typographical error, wherein the method of treatment now recites "administration to a subject in need of such treatment." Applicants have amended claims 45 and 46 to recite ranges for the diameter of the claimed human liver progenitors. Support for the above amendments and new claims 47 and 48 may be found throughout the specification as originally filed, notably at page 11, page 12, lines 2-12, lines 18-22, page 36, lines 12-14, page 71, lines 14-16, and claims 1 and 7-8. Applicants respectfully request entry of the amendments and remarks made herein into the file history of the present application.

At page 2 of Paper 14, the disclosure is objected to for allegedly failing to comply with the requirements set forth in 37 C.F.R. §§ 1.821-1.825. Applicants submit herewith substitute sheets of the paper copy of the Sequence Listing as originally filed pursuant to 37 C.F.R. § 1.825(a). Support for the amendments made by substitute sheets may be found at pages 1-14 of the Sequence Listing, as originally filed. Applicants respectfully request entry of the substitute sheets into the file history of the present application.

1. 35 U.S.C. § 102

a. The rejection of claims 12-19 for lack of novelty over Muench *et al.* (1994) or Muench *et al.* (1997)

At page 19 of Paper No. 14, claims 12-19 remain rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Muench *et al.* (1994) or Muench *et al.* (1997) (collectively, "Muench"). The Examiner characterizes Muench as disclosing a method for the isolation of human fetal liver progenitors using density centrifugation followed by negative immunoselection. Applicants respectfully traverse the rejection. Applicants respectfully submit that Muench does not anticipate claims 12-19, as amended.

Various subpopulations of progenitors are found in human liver tissue, including hepatic progenitors, hematopoietic progenitors and mesenchymal progenitors. *See* page 1, lines 3-6. The present invention is related to hepatic progenitors, pluripotent cells that give rise to hepatocytes and biliary cells. *See* page 11, lines 18-22. The hepatic progenitors of the present invention may be separated from other cells by using disclosed methods of debulking, such as low-speed centrifugation, to remove mature liver cells. *See* page 26, lines 13-20 and page 55, lines 5-11. The present invention takes advantage of the fact that mature liver cells are larger and more dense than immature progenitors. As a result, hepatic progenitors remain at or near the top of a density gradient after low speed centrifugation, whereas mature liver cells are found in the pellet. Example 4 discloses the isolation of liver progenitors using exemplary density centrifugation at 70 x g for 4 minutes and 100 x g for 5 minutes. *See* page 54, lines 22-24. Mature liver cells are found in the pellet under such exemplary conditions of density centrifugation, and the immature cells remain suspended.

Applicants respectfully submit that the methods disclosed by Muench for isolating progenitors are different from the method of claims 12-19, as amended. Applicants respectfully note that Muench describes centrifugation methods significantly different from the debulking methods disclosed in the present application. For example, Muench (1994) discloses the isolation of "light density" progenitors using density centrifugation at 1,000 x g for 25 minutes. *See* Muench (1994), page 3171, left-hand column. Under such conditions, both mature cells and immature cells are pelleted, thus failing to separate mature cells from immature cells.

Moreover, Applicants respectfully note that Muench (1994) and Muench (1997) do not describe the isolation of *hepatic* progenitors. Instead, Muench (1994) and Muench (1997) describe the isolation of other classes of progenitors from human fetal liver tissue, such as *hematopoietic* progenitors. *See* Muench (1994), page 3175, left-hand column; Muench (1997), page 1365, left-hand column.

As amended, claims 12-19 are directed to the isolation of hepatic progenitors from human liver tissue by a method that separates mature cells from immature cells. In view of the fact that Muench (1994) and Muench (1997) disclose methods that fail to achieve the separation of mature cells from immature cells and which lead to the isolation of different classes of progenitors, Applicants respectfully submit that the rejection of claims 12-19 under 35 U.S.C. § 102(b) has been overcome and withdrawal thereof is respectfully requested.

b. The rejection of claims 21-23 and 42-44 under 35 U.S.C. § 102(b) as being anticipated by Muench *et al.* (1994) or Muench *et al.* (1997)

At page 20 of Paper No. 14, claims 21-23 and 42-44 remain rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Muench *et al.* (1994) or Muench *et al.* (1997). The Examiner characterizes Muench as disclosing the isolation of human fetal liver progenitors that express various surface markers present on certain progenitors of the present invention. Applicants respectfully traverse the rejection. Applicants respectfully submit that Muench does not anticipate claims 21-23 and 42-44, as amended.

While hepatic progenitors and hematopoietic progenitors may have common cell surface antigens, Muench and Muench never disclose, teach or suggest that they had isolated hepatic progenitors. If anything, Muench and Muench had isolated only hematopoietic progenitors. Similar to remarks above, Applicants have amended claims 21-23 and 42-44 to be directed to hepatic progenitors. In view of the cited references failing to disclose hepatic progenitors, Applicants respectfully submit that the rejection of claims 21-23 and 42-44 under 35 U.S.C. § 102(b) has been overcome and withdrawal thereof is respectfully requested.

c. The rejection of claims 12-15, 18-23 and 42-44 under 35 U.S.C. § 102(b) as being anticipated by Craig *et al.*

At page 21 of Paper No. 14, claims 12-15, 18-23 and 42-44 remain rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Craig *et al.* ("Craig"). The Examiner characterizes Craig as disclosing the isolation of human hematopoietic progenitor cells derived

from human fetal liver cells using low density centrifugation, wherein the progenitor cells express various surface markers present on certain progenitors of the present invention. Applicants respectfully traverse the rejection. Applicants respectfully submit that Craig does not anticipate claims 12-15, 18-23 and 42-44, as amended.

As described above, Applicants have amended claims 12-15, 18-23 and 42-44 to be directed to human hepatic progenitors. In view of Craig's failure to disclose the isolation of human hepatic progenitors, Applicants respectfully submit that the alleged anticipation of claims 12-15, 21-23 and 42-44 under 35 U.S.C. § 102(b) has been overcome and withdrawal thereof is respectfully requested.

d. The rejection of claims 11, 20-26 and 42-44 under 35 U.S.C. § 102(e) as being anticipated by Farris *et al.*

At page 21 of Paper No. 14, claims 11, 20-26 and 42-44 remain rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Farris *et al.* ("Farris"). The Examiner characterizes Farris as disclosing the preparation and isolation of a liver cluster of less than 10 cells comprising a liver stem cell and a hepatocyte, and a primary liver stem cell derived from human liver tissue. Applicants respectfully traverse the rejection. Applicants respectfully submit that Farris does not anticipate claims 11, 20-26 and 42-44 as amended.

The Examiner characterized Farris as allegedly disclosing the isolation of a doublet consisting of a hepatocyte and a stem cell from human liver. Farris discloses the alleged isolation of a stem cell, which is defined as "an undifferentiated cell that differentiates into a mature functional hepatocyte or bile duct cell." *See* column 1, lines 37-39. Farris discloses that the isolated cells purported to be stem cells "share many cell makers with other liver cells [but] are distinguished from oval cells and other putative stem cells by virtue of their tight associations with a hepatocyte." *See* column 4, lines 41-44. Applicants respectfully submit that while Farris may have demonstrated proliferative characteristics, he has demonstrated neither pluripotent nor hepatic characteristics. Pluripotency (the capacity to give rise to hepatocytes and biliary cells) is a particularly important characteristic, which is needed to confirm that the cells are in fact *hepatic stem* cells (and not, for example, *hematopoietic stem* cells).

Farris allegedly confirms that the isolated cells are proliferative by exposing the liver to the carcinogen bromouridine and showing cellular incorporation of bromouridine by the isolated

cells. *See* column 7, lines 10-35. Even if, *arguendo*, Farris shows that the isolated cells are proliferative, Applicants respectfully submit that Farris does not provide any support that the isolated cells are pluripotent. The failure to confirm that the isolated cells are pluripotent would not allow one of ordinary skill in the art to reasonably conclude that the isolated cells are in fact stem cells and that they are hepatic stem cells. In view of claims 11, 20-26 and 42-44 being limited to hepatic pluripotent progenitors, Applicants respectfully submit that rejection of claims 11, 20-26 and 42-44 under § 102(e) has been overcome and withdrawal thereof is respectfully requested.

2. 35 U.S.C. § 103

a. The rejection of claims 1-6, 8, 12-19 and 45-46 under 35 U.S.C. § 103(a) as being obvious over Reid in view of Naughton

At page 24 of Paper 14, claims 1-6, 8, 12-19 and 45-46 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over U.S. Patent No. 6,069,005 ("Reid") in view of U.S. Patent No. 5,559,022 ("Naughton"). Applicants respectfully traverse the rejection. Applicants respectfully submit that claims 1-6, 8, 12-19 and 45-46, as amended, are not nonobvious over the cited references.

As mentioned above, one aspect of the present invention is related to the isolation of hepatic progenitors by using disclosed methods of debulking, such as low-speed centrifugation, to remove mature liver cells while retaining immature cells. As amended, claims 1-6, 8, 12-19 and 45-46 are directed to the preparation of a composition comprising human liver progenitors based on exclusion of mature liver cells taking advantage of the differences between progenitors and mature cells in cell size, buoyant density, or a combination thereof. The cited references fail to disclose, teach, or suggest any of the claimed methods of debulking. Hence, Applicants respectfully submit that the rejection of claims 1-6, 8, 12-19 and 45-46 under 35 U.S.C. § 103(a) has been overcome and withdrawal thereof is respectfully requested.

b. The rejection of claims 1 and 9 under 35 U.S.C. § 103(a) as being obvious over Reid in view of Naughton and further in view of Craig

At page 26 of Paper No. 14, claims 1 and 9 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Reid in view of Naughton and further in view of Craig *et al.* The teachings of Craig do not cure the above-discussed deficiency of Reid and Naughton. Thus, the proposed combination fails to disclose, teach, or suggest the isolation of the claimed progenitors based on cell size, buoyant density, or a combination thereof. Accordingly, Applicants respectfully submit that the rejection of claims 1 and 9 under 35 U.S.C. § 103(a) has been overcome and withdrawal thereof is respectfully requested.

c. The rejection of claims 21 and 38 under 35 U.S.C. § 103(a) as being obvious over Muench *et al.* (1994) or Muench *et al.* (1997) in view of Reid

At page 27 of Paper No. 14, claims 21 and 38 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Muench et al. (1994) or Muench et al. (1997) in view of Reid (USP 5,789,246). As discussed above, the disclosures of Muench et al. fail to teach the separation of mature cells from immature cells and only disclose the alleged isolation of *hematopoietic* progenitors. As amended, claim 21 recites that the claimed enriched population of human hepatic pluripotent progenitors, their progeny, or more mature forms thereof, exhibit one or more markers indicative of expression of *full length* alpha-fetoprotein, *full length* albumin, or both. Adequate support for the amendment is found on page 48, lines 2-5, of the specification as filed, which describes hepatic cell lines as expressing a transcript of the "whole coding region" (i.e., full length) of alpha-fetoprotein. See, also, page 47, line 20 to page 48, line 11. By contrast, the inventors found that a truncated form of alpha-fetoprotein, which is missing the N-terminal portion of the protein, is expressed by a hematopoietic cell line. Similar results were observed for albumin. See, page 48, lines 12-24, of the specification as filed.

Moreover, the proposed combination with Reid fails to remedy the deficiencies of either of the Muench references because the secondary reference fails to inform of the existence of the full length versus truncated forms of alpha-fetoprotein and albumin in hepatic versus hematopoietic lineages, respectively. Hence, claim 21 cannot reasonably be held obvious over the proposed combination. It follows, then, that claim 38, which contains all the limitations of claim 21, is likewise not obvious over the cited references.

The rejections having been overcome, Applicants respectfully request withdrawal of the rejections and favorable reconsideration of the rejected claims.

3. 35 U.S.C. § 112, First Paragraph

At page 3 of Paper No. 14, claims 1-9, 12-19, 27-35, 39 and 45-46 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was allegedly not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

a. The rejection of claims 1-9, 12-19, 27-34, 39 and 45-46 under 35 U.S.C. § 112, first paragraph, for lack of enablement

The Examiner contends that the specification allegedly fails to teach how to use the inventive human liver progenitor cells in treating liver dysfunction or liver diseases. In supporting this contention, the Examiner alleges that the specification fails to demonstrate that by administering the inventive human liver progenitor cells, a patient is "treated for symptoms associated with liver dysfunction or diseases." The Examiner also asserts that it would require undue experimentation for the skilled artisan to use the instant claimed invention because of the alleged inherent unpredictability of cell transplantation. In effect, the Examiner asserts that the "advantage" offered by administering the inventive cells to a patient cannot be "correlated" with "a therapeutic outcome." Applicants respectfully traverse the rejection. Applicants respectfully submit that the Examiner has misapplied the legal standard for enablement under 35 U.S.C. § 112, first paragraph.

In the instant application, Applicants provide an extensive disclosure of treating liver dysfunction or diseases using the inventive liver progenitor cells. Applicants respectfully draw the Examiner's attention to page 15 line 23 *et seq.*, page 16 line 3 *et seq.*, page 16 line 26 *et seq.*, page 22 line 16 *et seq.*, page 13 line 22 *et seq.* and page 42 line 17 *et seq.*, which are directed to

the treatment of liver dysfunction or diseases. Furthermore, as discussed in Applicants' response to the previous Office Action, administration of suspensions of cultured cells in general, and hepatocytes in particular, to a subject in need thereof, is not a complicated procedure, and is well-known and practiced in the art. The instant specification further provides guidance regarding suitable cell numbers, the advantages of small cell size for minimizing embolus formation, the advantages of hepatic progenitors *vis-a-vis* hepatocytes as resistant to immunological rejection, and increased proliferative capacity.

The Examiner does not dispute that the specification discloses how to make the claimed liver progenitor cells, nor does the Examiner question that administering the inventive human liver progenitor cells offers distinct *advantages* to the treated patient. Furthermore, the Examiner does not dispute that administration of cultured cells to a patient is routine, and the skilled artisan routinely engages in formulation of pharmaceutical compositions comprising cultured cells. While it is expected that a certain amount of experimentation is needed to achieve optimal effects depending on the specific disease or dysfunction to be treated, the patient's condition and other factors, it is well established that necessary or even complex but routine experimentation does not amount to "undue experimentation" for purposes of an enablement analysis. *See, e.g.* MPEP § 2164.01 ("The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *See In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), aff'd. sub nom., *Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). *See also In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976)).

In short, the Examiner does not assert that the specification fails to teach how to make and use the invention. Instead, the Examiner alleges that the "therapeutic utility" in the rejected claims was not credible, or not achievable without undue experimentation. In other words, the Examiner asserts that it would require undue experimentation to determine the "appropriate dosage," "exact site" and "frequency of administration," to eliminate potential adverse host immune reactions, to ensure that the cells be properly "engrafted, proliferated and differentiated," and that the cells "persist in a treated subject for a sufficient time to provide a

stable, long-term *in vivo* expression of the therapeutic transgene" such that a "therapeutic outcome" is achieved. *See, e.g.,* pages 5 and 12 of Paper No. 14. The criticism by the Examiner of the disclosure of Example 10 also centers around the notion that there has not been established a "correlation" or "nexus" between any "treatment" and the liver parenchymal cell regeneration observed, and that linking this observation to any future human therapeutic treatment would be an inappropriate "extrapolation."

In effect, the Examiner imposes a utility requirement that the claimed method of treatment be *fully effective and safe* for patentability purposes. Apparently, in the Examiner's mind, effective treatment must be, or at least close to, a cure of the disease or condition. Any thing less, no matter how advantageous or beneficial, would be inadequate. As a consequence of this improperly heightened utility requirement, the Examiner concludes, equally improperly, that the instant specification fails to enable the claimed invention, because, in order to achieve this "fully effective and safe" treatment or therapeutic outcome, the experimentation needed would be undue.

Applicants respectfully submit first that, as discussed above, necessary or even complex experimentation is not necessarily undue. As is well known to the skilled artisan, dosage determination and formulation of known pharmaceutical compositions, although often tedious and complex, are routine and do not require undue experimentation.

More importantly, Applicants respectfully submit that the Examiner's assertions are contrary to well-established legal requirements for both utility and enablement analyses. In fact, the MPEP, in summarizing various court decisions, specifically admonishes that the "therapeutic utility sufficient under the patent laws is not to be confused with the requirements of the FDA with regard to safety and efficacy of drugs to [be] marketed in the United States." MPEP § 2107.01(III). The MPEP then continues, by citing *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995), that:

> FDA approval, [] is not a prerequisite for finding a compound useful within the meaning of the patent laws. *Scott* [*v. Finney*], 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 [(Fed.Cir. 1994)]. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be

> administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.
>
> *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995). Accordingly, Office personnel should not construe 35 U.S.C. 101, under the logic of "practical" utility or otherwise, to require that an applicant demonstrate that a therapeutic agent based on a claimed invention is a safe or fully effective drug for humans. See, e.g., *In re Sichert*, 566 F.2d 1154, 196 USPQ 209 (CCPA 1977); *In re Hartop*, 311 F.2d 249, 135 USPQ 419 (CCPA 1962); *In re Anthony*, 414 F.2d 1383, 162 USPQ 594 (CCPA 1969); *In re Watson*, 517 F.2d 465, 186 USPQ 11 (CCPA 1975).

MPEP § 2107.01(III) (*emphases added*).

The Examiner has impermissibly required that the claimed invention be fully effective and safe, contrary to the well-established legal standard established by the courts and the PTO. When the proper standard for utility requirement analysis is applied, it is evident that the claims are enabled to their full scope, because the instant specification discloses how to make the claimed human liver progenitor cells, how these cells can be administered to a subject in need thereof, and provided *in vitro* and animal testing data demonstrating that administration of the cells to a subject provided expected benefits to the subject. Accordingly, Applicants respectfully submit that for this reason alone, the rejection of claims 1-9, 12-19, 27-34, 39 and 45-46 under 35 U.S.C. § 112, first paragraph, for lack of enablement is improper and cannot be sustained.

b. The rejection of claim 35 under 35 U.S.C. § 112, first paragraph, for lack of enablement

Claim 35 recites a method of treatment using the inventive human liver progenitor cells harboring exogenous nucleic acid. Because the difference between claim 35 and claim 27 is that the cells in claim 35 additionally harbor exogenous nucleic acid, the above discussion regarding the rejections of claims 1-9, 12-19, 27-34, 39 and 45-46 establishes that all aspects of claim 35 are enabled with the exception of the exogenous nucleic acid element. In this regard, the Examiner asserts that (i) the specification fails to disclose any specific vector used for treating a specific disease, (ii) there is a general lack of suitable vectors to achieve "long-term

and stable transgene expression," and (iii) *in vivo* therapeutic effects of gene therapy vectors are not "always predictable," and much more fundamental research is needed.

The proper legal standard for enablement analysis is whether a person skilled in the relevant art could have made *any* vector and used it in combination with the claimed human liver progenitor cells for treating diseases without undue experimentation at the time of the filing. The Applicants respectfully submit that the instant application provides detailed disclosure regarding how to make hepatic precursors with an exogenous gene of interest, including a specific example of genetic modification of hepatic precursors with the urokinase gene, including the effects of the transfection. The Examiner's attention is respectfully directed to human hepatic progenitors, their progeny, or more mature forms that harbor exogenous nucleic acid, including: page 14 line 11, page 22 line 22, page 23 line 1, page 42 line 3 *et seq.*, page 42 line 13, page 42 line 17 *et seq.*, page 42 line 26 *et seq.*, and Example 10 directed to use of the urokinase gene.

The Examiner does not make any assertion that the disclosure is not enabling in this regard, but again focuses on how the available vectors in the art might not be fully effective. Because, for the same reasons discussed above, this is an improper legal standard, the Applicants respectfully submit that this rejection of claim 35 under 35 U.S.C. § 112, first paragraph, is improper and should be withdrawn.

4. 35 U.S.C. § 112, Second Paragraph

a. The rejection of claims 1-9, 11-20, 27-35 and 45-46 under 35 U.S.C. § 112, second paragraph

At page 16 of Paper 14, claims 1-9, 11-20, 27-35 and 45-46 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regards as the invention. Applicants respectfully traverse the rejection.

At page 16 of Paper 14, the Examiner rejects claims 1 and 12 on the grounds that the specification allegedly does not provide a standard for ascertaining the requisite degree of the term "substantially," and one of ordinary skill in the art would allegedly not be reasonably apprised of the scope of the invention. In order to clarify the meaning of the instant claims and to expedite prosecution, Applicants have removed the recitation of "substantially single", thereby

rendering these rejections moot. Applicants respectfully submit that the amendments do not limit the scope of claims 1 and 12.

At page 16 of Paper 14, the Examiner similarly rejects claim 1 on the basis that the terms "relatively large size" and "relatively small size" allegedly render the claim indefinite. In order to clarify the meaning of the instant claim and to expedite prosecution, Applicants have removed the recited terms, thereby rendering the rejection moot. Once again, the Applicants respectfully submit that the amendments do not limit the scope of claim 1.

The Examiner requests clarification regarding what is encompassed by the phrase "[a] method of providing a composition" in claims 1 and 12. In order to clarify the metes and bounds of the instant claims, Applicants have amended claims 1 and 12 to recite "[a] method of preparing a composition." Applicants respectfully submit that the amendments do not limit the scope of claims 1 and 12.

The Examiner also requests clarification regarding what is encompassed by the phrase "in a subject in need thereof" in claims 27 and 35. Applicants have amended claims 27 and 35 to recite "comprising administering to a subject in need of such treatment" in order to clarify the metes and bounds of the claims. Applicants respectfully submit that the amendments do not limit the scope of claims 1 and 12. Accordingly, in view of the amendments to claims 1, 12, 27 and 35, Applicants respectfully submit that the rejection of claims 1-9, 11-20, 27-35 and 45-46 under 35 U.S.C. § 112, second paragraph, has been overcome and withdrawal thereof is respectfully requested.

5. New Matter

The Examiner rejected claim 45 for containing subject matter which was not described in the specification in such a way as to convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Applicants have amended claim 45 to recite "[t]he method of claim 1 in which the human liver progenitors have a diameter between 5 and 15 microns." Literal support in the originally filed specification for retaining immature cells with a diameter of 5-15 microns may be found at page 71, lines 14-15. In view of the foregoing, the Applicants respectfully submit that the Applicants contemplated and had possession of the claimed invention at the time the application was filed.

6. Double Patenting

a. The provisional obviousness-type double patenting rejection of claims 27-33 and 35

Claims 27-33 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 59-77 of copending Application No. 09/154,224 (the "'224 Application").

Claim 35 was provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 21-39 of copending Application No. 09/534,487 (the "'487 Application").

In light of the fact that the conflicting claims have not in fact been patented and that this is a provisional rejection, the Applicants respectfully request that the rejection be stayed pending allowance of the '224 Application and allowance of the '487 Application. Applicants will consider the possibility and propriety of filing a terminal disclaimer upon the allowance of the '224 Application or upon the allowance of the '487 Application.

CONCLUSION

In view of the above remarks, the Applicants respectfully submit that the instant application is in good and proper order for allowance and early notification to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite prosecution of the instant application, the Examiner is encouraged to call the undersigned at (202) 625-3838.

Respectfully submitted,

KATTEN MUCHIN ZAVIS ROSENMAN

By: 
Gilberto M. Villacorta, PH.D.
Registration No.: 34,038

Dated: September 30, 2002
KATTEN MUCHIN ZAVIS ROSENMAN
1025 Thomas Jefferson Street, NW
East Lobby, Suite 700
Washington, DC 20007-5201
(202) 625-3838 (Telephone)
(202) 298-7570 (Fax)